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Epidemiology of sepsis in ICUs of Western China

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ABSTRACT

Objectives: To investigate the relationship between sepsis prevalence and disease types in intensive care units (ICUs), as well as the effect of knowledge of the health care workers about the sepsis guidelines on sepsis morbidity and mortality.

Methods: A one-day cross-sectional survey was conducted in five ICUs in the cities of Chongqing and Guizhou, China. The included patients were divided into three groups: the internal medicine group (Group A), surgery group (Group B), and trauma group (Group C). Sepsis was diagnosed by the 2012 Sepsis Guidelines, and the prevalence and 28-day mortality were statistically analyzed. The relationship between the knowledge of health care workers about sepsis and morbidity and mortality was analyzed.

Results: Among the enrolled 71 patients, the sepsis prevalence rate was 81.5%, 66.7%, and 87.0% in Groups A, B, and C, respectively. In total, the 28-day mortality rate was 36.4%, 42.9% and 20.0% in Groups A, B, and C, respectively, indicating no significant difference. The sepsis prevalence was 66.7%, 90.0%, 90.9%, 100.0% and 76.9% in the five ICUs. The average cognitive score of each hospital was 68.5 ± 15.4 , 65.7 ± 16.7 , 69.0 ± 23.3 , 25.0 ± 8.4 , and 61.4 ± 19.9 points in the five ICUs. Cognitive scores were not associated with prevalence of sepsis, but they were negatively related with sepsis mortality.

Conclusions: Sepsis prevalence and mortality are not associated with diseases types within ICUs, but the knowledge of sepsis of health care workers is associated with the prognosis of sepsis patients.

1. Introduction

Sepsis remains a continuing challenge for clinicians and medical workers worldwide. Sepsis is the leading cause of death in non-cardiac intensive care units (ICUs)^[1] and is the tenth highest cause of death^[2]. It has been estimated that in the United States, the incidence of severe sepsis in hospitalized patients is 2%^[3], and the prevalence rate is 10% in ICUs^[4].

There are more than 1.1 million patients diagnosed with sepsis each year, with an annual cost of 24.3 billion dollars^[1,3]. The incidence of sepsis has increased by 1.5% annually, and the number of sepsis patients is expected to reach 1 million in 2020^[3,5,6]. Despite the decline in the number of patients, its mortality is very high. The mortality rate of severe sepsis patients is approximately 25%, and the mortality of septic shock is approximately 50%^[7].

Sepsis has varying characteristics in different diseases. In surgical patients, sepsis remains one of the leading causes of morbidity and mortality^[8]. Surgical patients with sepsis in the United States account for one-third of patients^[3]. The American College of Surgeons National Surgical Quality Improvement Program database reported that the number of sepsis and septic shock cases is 10 times more than the number of myocardial infarction and pulmonary embolism cases during the peri-operative period^[9]. Trauma is the leading cause of death in young adults, accounting for

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The study protocol was performed according to the Helsinki declaration and approved by the Ethics Committee of the Third Military Medical University. Informed written consent was obtained from all the patients in the study.

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approximately 10% of trauma deaths around the world^[10]. Sepsis is the main cause of death in trauma patients^[10]. Treatments such as airway management, blood transfusion, and surgery can save the lives of trauma patients and reduce mortality. However, patients have become increasingly dependent on invasive devices and technologies, which has increased the risk of infection and sepsis. Epidemiology and clinical data about sepsis of critically ill trauma patients are very limited. We initially conducted the multi-center epidemiology study about sepsis of trauma patients in China and also initially compared the epidemiology of sepsis between trauma patients and patients with other diseases, which is important for studying the characteristics of sepsis in different diseases.

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) first proposed the definition and diagnostic criteria for the systemic inflammatory response syndrome (SIRS) and sepsis^[10]. To better reflect the pathophysiological changes of sepsis, and to improve the survival rate of critically ill patients, ACCP, SCCM, the European Society of Intensive Care Medicine (ESICM) and the American Thoracic Society (ATS) modified the definition of severe sepsis based on evidence-based medicine in 2001 and 2012. Since the first guidelines were published in 1992, the concept of sepsis has been acknowledged and emphasized worldwide, and sepsis has been treated in accord with these guidelines, which can help to achieve early diagnosis and early treatment of sepsis and reduce mortality of sepsis^[11–13]. It has been found that in the emergency department and ICU, the emphasis on early intervention of sepsis could reduce mortality^[14]. Understanding the relationship between knowledge about sepsis guidelines and sepsis can help to further specify and improve the guidelines.

In this study, we aimed to compare the prevalence and 28-day mortality of sepsis among the ICUs of grade-3 hospitals in Western China and to study the relationship between the knowledge of health care workers about sepsis and the updated sepsis guidelines.

2. Materials and methods

2.1. Study subjects

The inclusion criteria included age greater than 18 years and the patients being hospitalized in the ICU for more than 24 h.

2.2. Research methods

This study was approved by the Ethics Committee of the Third Military Medical University.

Survey time: June 2014 to August 2014, one day for each hospital.

Specific time: Hospital 1: 8:00 a.m., June 16, 2014 to 8:00 a.m., June 17, 2014; Hospital 2: 8:00 a.m., July 14, 2014 to 8:00 a.m., July 15, 2014; Hospital 3: 8:00 a.m., July 23, 2014 to 8:00 a.m., July 24, 2014; Hospital 4: 8:00 a.m., July 26, 2014 to 8:00 a.m., July 27, 2014; Hospital 5: 8:00 a.m., July 31, 2014 to 8:00 a.m., August 1, 2014.

The research team consisted of two trauma surgeons and two ICU doctors. All team members were trained in the diagnostic criteria for investigation, survey methods, questionnaire completion and data input prior to the survey.

A one-day cross-sectional survey was conducted. The questionnaire was completed based on clinical data collected from the patients' medical and nursing records and medical history. Patients were divided into Groups A, B, and C in accordance with their disease type (internal medicine, surgery, and trauma, respectively). Infection was diagnosis based on laboratory parameters [white blood cell (WBC), procalcitonin, D-glucan, bacterial culture, *etc.*], radiology (chest X-ray, CT, *etc.*), and clinical symptoms (fever, difficulty breathing, abdominal pain secretions or increased drainage fluid and purulent material drainage). We used the worst data to evaluate and diagnose sepsis according to the 2012 international guidelines, followed by the 28-day mortality. Additionally, in each surveyed hospital, we surveyed the knowledge of ICU doctors who had greater than five years of working experience in the ICU about the sepsis guidelines.

The survey is divided into four parts: (1) demographic data and clinical characteristics of patients: average age, gender, admission ISS score, admission ICU APACHE II, GCS, sepsis-related organ failure assessment (SOFA) scores, underlying diseases (cardiac dysfunction, neurological dysfunction, respiratory insufficiency, renal insufficiency, hepatic insufficiency, diabetes), and the number of sepsis, severe sepsis, septic shock and 28-day death sepsis patients in each group; (2) infection data: infection site (lungs, urinary tract, abdomen, surgical wounds, *etc.*), and pathogenic bacteria (Gram-negative bacteria, Gram-positive bacteria, fungi); (3) basic information about the five surveyed hospitals, diagnosis and prognosis of the included sepsis patients and knowledge about the sepsis guidelines; (4) sepsis guidelines questionnaire: sepsis cause, sepsis diagnostic criteria, and sepsis treatment recommendations. The questionnaire consists of 14 questions with a total of 100 possible points.

2.3. Definitions

Pneumonia was defined with the following criteria: fever ($> 38^{\circ}\text{C}$), leukocytosis, chest radiograph with new infiltrate, increased sputum volume, and decreased oxygen index.

Abdominal infection was identified by the symptoms of abdominal distension and pain, drainage of purulent material from the wound, and enteral nutrition intolerance in patients who had recently undergone abdominal surgery.

Bacteremia was defined as a positive blood culture, excluding isolates that were thought to be contaminants.

Urinary tract infections: Urine WBC $> 10/\text{high magnification}$ or urine culture bacteria $> 100\,000/\text{mL}$.

Wound infection was defined as purulent drainage or aggressive treatment with antibiotics.

Chronic disease: Data related to pre-existing diseases were collected by reviewing the medical record, including admission history, physician consultations, and operative, laboratory, radiology, and autopsy reports. Diabetes was defined in patients who were insulin-dependent or who required oral hypoglycemic agents. Heart, liver, kidney, and respiratory insufficiency were

defined as a single organ SOFA score greater than two points on admission^[5].

The consensus definition for sepsis was based on the 2012 International Sepsis Guidelines^[13].

2.4. Statistical analysis

Data are expressed as the mean \pm SEM values. Non-normally distributed measurement data are expressed as the median (interquartile range). Rates were compared using the *Chi*-square test, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SAS9.13 software.

3. Results

A total of 71 patients were enrolled, with 27, 21, and 23 patients in Groups A, B, and C, respectively. The average age, gender, ISS score, APACHE II score on ICU admission, SOFA and GCS scores, hospitalization days, underlying diseases, sepsis diagnosis, and the numbers of 28-day deaths are shown in Table 1.

Twenty-two patients in Group A had sepsis, 14 in Group B, and 20 in Group C, with the respective prevalence rates of sepsis being 81.5%, 66.7%, and 87.0%. There were 56 total sepsis patients, with a prevalence rate of 78.9%. Eighteen severe sepsis patients were in Group A, 12 in Group B, and 16 in Group C, with the prevalence rate of severe sepsis in Groups A, B, and C being 66.7%, 57.1%, and 70.0%, respectively. There were 46 severe sepsis patients in total, with a prevalence of 64.8%. Eight patients died in Group A, 7 in Group B, and 3 in Group C, and the 28-day death rates were 36.4%, 42.9%, and 20% in Groups A, B, and C, respectively. In sum, 18 patients died, with the mortality rate being 31.1%. There was no significant difference

in sepsis prevalence, severe sepsis prevalence and the 28-day death rate among the three groups.

The infection data (infection sites, pathogenic bacteria) are shown in Table 2. The most common infection site was the lungs, followed by the urinary tract, and the most common pathogenic bacteria for ICU patients was Gram-negative bacteria.

The relevant information about the surveyed hospitals, diagnosis and prognosis of the included sepsis patients and knowledge about the sepsis guidelines are shown in Table 3.

The number of patients included in the five hospitals was 30, 10, 11, 7, and 13, respectively. The average hospital stay in the five hospitals was 73.4, 65.0, 10.0, 7.1, and 18.9 days, respectively, with an average of 52.2 days. The number of sepsis patients in the five hospitals was 20, 9, 10, 7, 10, and 56, respectively, and the prevalence rates were 66.7%, 90.0%, 90.9%, 100%, 76.9%, and 78.9%, respectively. The number of severe sepsis patients within the five hospitals was 19, 6, 9, 5, and 7, respectively, and the prevalence rates were 63.3%, 60.0%, 81.8%, 71.4%, and 53.8%, respectively. The number of patients who died within 28 days was 4, 3, 2, 4, and 5, respectively, with mortality rates of 13.3%, 30.0%, 18.2%, 57.1%, and 30.8%, respectively. A total of 40 ICU medical workers participated in the survey, among which 17, 7, 5, 4, and 7 medical workers participated in each hospital, respectively. The average questionnaire score for knowledge about the sepsis guidelines was 68.5 ± 15.4 , 65.7 ± 16.7 , 69.0 ± 23.3 , 25.0 ± 8.4 , and 61.4 ± 19.9 points, respectively. Statistical analysis was performed on the cognitive questionnaire scores, prevalence of sepsis and severe sepsis and 28-day mortality. Cognition scores were negatively related with sepsis-related mortality.

The 14 questions and the number of health care workers who answered the questions correctly are shown in Table 4. Questions that had a correct response rate of greater than 80% included: the most common cause of sepsis and fluid resuscitation volume. Questions that had a correct response rate of 60–80% included: SIRS diagnostic criteria, procalcitonin as a diagnostic indicator, fungal infection diagnostic tests, CRRT treatment for unstable blood flow patients, preferred vasopressors for septic shock, and sepsis-caused ARDS ventilation strategy. Questions with a correct response rate of less than 60% included: the year when the latest sepsis guidelines were developed, application of hydrocortisone for septic shock, antibiotic usage time for sepsis, preventive stress

Table 1

Basic and clinical characteristics of the included patients.

| Characteristics | Medicine (n = 27) | Surgery (n = 21) | Trauma (n = 23) | Total (n = 71) |
|----------------------------|----------------------|---------------------|--------------------|-------------------|
| Mean age | 66.4 \pm 15.9 | 62.7 \pm 15.4 | 48.3 \pm 14.8 | 59.5 \pm 17.0 |
| Male | 19 (70.4%) | 14 (66.7%) | 16 (69.6%) | 49 (69.0%) |
| ISS | N/A | N/A | 25.9 \pm 9.7 | N/A |
| APACHE II | 23.7 \pm 8.3 | 20.4 \pm 5.9 | 18.8 \pm 9.8 | 21.1 \pm 8.1 |
| SOFA | 8.7 \pm 4.4 | 7.5 \pm 4.2 | 5.7 \pm 3.1 | 7.5 \pm 4.1 |
| GCS | 11.9 \pm 4.4 | 12.7 \pm 4.3 | 11.2 \pm 4.0 | 11.3 \pm 4.4 |
| ICU length of stay (day) | 10 (3–19) | 10 (6–70) | 9 (2–22) | 8 (2–20.5) |
| Underline diseases [n (%)] | | | | |
| Heart dysfunction | 5 (18.5%) | 3 (14.3%) | 2 (8.7%) | 10 (14.1%) |
| Nerve dysfunction | 5 (18.5%) | 4 (19.0%) | 3 (13.0%) | 12 (16.9%) |
| Respiratory dysfunction | 8 (29.6%) | 4 (19.0%) | 2 (8.7%) | 14 (19.7%) |
| Renal dysfunction | 3 (11.1%) | 0 (0%) | 0 (0%) | 3 (4.2%) |
| Liver dysfunction | 2 (7.4%) | 0 (0%) | 0 (0%) | 2 (2.8%) |
| Diabetes | 6 (22.2%) | 3 (14.3%) | 3 (13.0%) | 12 (16.9%) |
| Sepsis | 22 (81.5%) | 14 (66.7%) | 20 (87.0%) | 56 (78.9%) |
| Severe sepsis | 18 (66.7%) | 12 (57.1%) | 16 (70.0%) | 46 (64.8%) |
| 28-day death patients | 8 (36.4%) | 7 (42.9%) | 3 (20.0%) | 18 (32.1%) |

Table 2

Infection-related data.

| Characteristics | | Medicine (n = 27) | Surgery (n = 21) | Trauma (n = 23) | Total (n = 71) |
|-----------------|----------------|----------------------|---------------------|--------------------|-------------------|
| Infection sites | Lung | 22 (81.5%) | 15 (71.4%) | 19 (82.6%) | 56 (78.9%) |
| | Urinary tract | 8 (29.6%) | 2 (9.5%) | 2 (8.9%) | 12 (16.9%) |
| | Abdomen | 0 (0%) | 9 (42.9%) | 1 (4.3%) | 10 (14.1%) |
| | Surgical wound | 0 (0%) | 2 (9.5%) | 3 (13.0%) | 5 (7.0%) |
| | Blood | 1 (3.7%) | 0 (0%) | 0 (0%) | 1 (1.4%) |
| Pathogens | Other | 0 (0%) | 1 (4.8%) | 2 (8.7%) | 3 (4.2%) |
| | G-bacteria | 12 (48.1%) | 10 (47.6%) | 9 (39.1%) | 31 (43.6%) |
| | G + bacteria | 2 (7.4%) | 2 (9.5%) | 1 (4.3%) | 5 (7.0%) |
| | Fungi | 3 (11.1%) | 2 (9.5%) | 0 (0%) | 5 (7.0%) |

Table 3

Basic information of the surveyed hospital, diagnosis and prognosis of sepsis patients, and questionnaire score of sepsis guidelines.

| Characteristics | Hospital 1 | Hospital 2 | Hospital 3 | Hospital 4 | Hospital 5 | Total |
|--|-------------|-------------|-------------|------------|---------------|-------------|
| Established year of hospital ICU | 1985 | 1987 | 1990 | 1990 | 2007 | |
| ICU type | Trauma ICU | Trauma ICU | Center ICU | Trauma ICU | Emergency ICU | |
| Hospital beds | 2400 | 680 | 2900 | 2900 | 2035 | |
| ICU beds | 41 | 12 | 12 | | 8 | |
| Survey time | 2014.6.17 | 2014.7.15 | 2014.7.24 | 2014.7.26 | 2014.8.1 | |
| Number of total patients | 37 | 12 | 12 | 8 | 16 | 85 |
| Number of excluded patients | 7 | 2 | 1 | 1 | 3 | 14 |
| Number of included patients | 30 | 10 | 11 | 7 | 13 | 71 |
| Mean hospitalization, day | 73.4 | 65.0 | 10.0 | 7.1 | 18.9 | 52.2 |
| Number of sepsis patients | 20 (66.7%) | 9 (90.0%) | 10 (90.9%) | 7 (100%) | 10 (76.9%) | 56 (78.9%) |
| Number of severe sepsis patients | 19 (63.3%) | 6 (60.0%) | 9 (81.8%) | 5 (71.4%) | 7 (53.8%) | 46 (64.8%) |
| 28-day death patients | 4 (13.3%) | 3 (30.0%) | 2 (18.2%) | 4 (57.1%) | 5 (30.8%) | 18 (23.4%) |
| Questionnaire score of sepsis guidelines | 68.5 ± 15.4 | 65.7 ± 16.7 | 69.0 ± 23.3 | 25.0 ± 8.5 | 61.4 ± 19.9 | 62.5 ± 20.6 |

Table 4

Questionnaire about knowledge of the 2012 sepsis guidelines.

| Questionnaire | Right | Wrong | Right-answer rate |
|---|-------|-------|-------------------------|
| 1. Common cause of sepsis | 37 | 3 | 92.5% (88.34%, 100.66%) |
| 2. The year to establish the updated guideline for treating severe sepsis and sepsis shock | 21 | 19 | 52.5% (37.02%, 67.98%) |
| 3. Guidelines recommend to use procalcitonin as a diagnostic marker of sepsis | 32 | 8 | 80.0% (67.60%, 92.40%) |
| 4. SIRS diagnostic criteria | 25 | 15 | 62.5% (47.50%, 77.50%) |
| 5. Diagnostic tests in high-risk severe sepsis patients with fungi infection | 32 | 8 | 80.0% (67.60%, 92.40%) |
| 6. Adult patients with septic shock can use hydrocortisone without considering hemodynamic stability | 18 | 22 | 45.0% (29.58%, 60.42%) |
| 7. Using at least 1 000 mL of liquid crystals within the first 4–6 h for the suspected hypovolemia patients | 35 | 5 | 87.5% (77.25%, 97.75%) |
| 8. Hemodynamically unstable patients are not recommended to use continuous renal replacement therapy | 32 | 8 | 80.0% (67.60%, 92.40%) |
| 9. Antibiotics application time for severe sepsis and septic shock | 16 | 24 | 40.0% (24.82%, 55.18%) |
| 10. The preferred vasopressors for septic shock | 24 | 16 | 60.0% (67.60%, 92.40%) |
| 11. Drugs recommended for preventive stress ulcer for severe sepsis/septic shock patients | 21 | 19 | 52.5% (37.02%, 67.98%) |
| 12. The number of blood culture specimens for severe sepsis/septic shock patients | 8 | 32 | 20.0% (7.60%, 32.40%) |
| 13. Liquid choices for liquid fluid resuscitation | 11 | 29 | 27.5% (12.74%, 42.26%) |

ulcer drug, the number of blood culture specimens, and liquid options for liquid resuscitation.

4. Discussion

This observational study aimed to provide data about sepsis morbidity and mortality in ICUs of Southwestern China. In this study, we found that the prevalence of sepsis was 78.9%, the prevalence of severe sepsis (including septic shock) was 64.8%, and sepsis mortality was 31.1% in grade-three hospitals of Southwestern China. A one-day cross-sectional study that included approximately 254 ICUs of Mexico showed that the prevalence of sepsis and severe sepsis were 16% and 17%, respectively^[15]. A one-day sepsis survey that included approximately 454 ICUs in Germany showed that the prevalence of sepsis and severe sepsis were 12.4% and 11.0%, respectively^[16]. A multi-center study of 198 ICUs from 24 European countries reported that the prevalence of sepsis and severe sepsis were 37% and 30%, respectively^[17,18]. Both prospective and retrospective epidemiological studies about sepsis have shown that the incidence of sepsis ranges from 6.3% to 14.6%. A multi-center sepsis epidemiological study of 22 ICUs in China indicated that the incidence of severe sepsis was 37.3%^[19]. The prevalence of sepsis in our study was significantly higher than that of other reports, which may be because the economic and medical conditions are more poorly developed in western regions.

In addition, sepsis is the main cause of death in surgical patients, and the peri-operative mortality of septic shock is higher than the sum of myocardial infarction and pulmonary embolism^[9]. Risk factors for the occurrence and death from sepsis and sepsis mortality include age greater than 60 years, requiring emergency surgery and underlying disease^[20]. Surgical abdominal sepsis is the most common source of infection for surgical patients, which is different from medical patients^[21]. An epidemiological study from a Brazil ICU showed that the incidence of severe sepsis was 5% and the mortality was 14.8% for surgical patients^[20]. Compared with medical and surgical patients, trauma patients had characteristics of younger average age and more invasive diagnosis and treatment. The prevalence, mortality and risk factors of sepsis for trauma patients are controversial. Wafaisade *et al.*^[22] conducted a 16-year research study in 166 trauma centers in Germany, and they reported that the incidence of post-traumatic sepsis was 10.2% and the mortality rate was 19.5%. Osborn *et al.*^[23] surveyed all of the trauma centers in Pennsylvania, and they reported that the sepsis incidence was 2% and the mortality rate was 23.1%. They also reported that the risk factors included ISS score, revised trauma score, low admission GCS score and underlying diseases. The reason for the low incidences of the abovementioned two studies may be that the study subjects were not trauma patients in the ICU. Compared to non-ICU patients, ICU patients have more severe disease conditions, more underlying diseases, and more invasive treatment, thus resulting in higher incidences of sepsis^[4,24].

In 2012, a study published in “Shock” journal compared the morbidity and mortality of sepsis among burn patients, trauma patients and other critically ill trauma patients, and the study reported that the sepsis prevalence of burn patients, trauma patients and other critically ill trauma patients were 2.4%–16.9%, 8%–42.5% and 19%–38%, respectively^[25]. Our study initially compared sepsis morbidity and mortality among the same kind of patients who had different types of admission, which is important for studying the epidemiology of sepsis caused by different diseases. In 1991, the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine re-defined the systemic inflammatory response (SIRS) and multiple organ dysfunction syndrome (MODS)^[26]. In 2001, it revised the primary definition and increased the list of signs and symptoms^[11]. This consensus definition is still nonspecific and allows variability, especially in the definition of organ insufficiency^[11]. Sepsis in different diseases has varying characteristics, and it also has different epidemiology, clinical features, and treatment. Therefore, using the same definition to determine the different types of sepsis may not truly reflect the pathophysiology of different diseases, and hence cannot achieve early diagnosis, early treatment purposes, and reduce its mortality. The sepsis guidelines proposed by ACCP, SCCM, ESICM and ATS have high sensitivity and low specificity, but they ignore the different characteristics of the individual disease sepsis, leading to increased misdiagnosis and missed diagnoses^[11,13,26,27]. This may be the reason why there was no difference in the sepsis prevalence among the three groups of patients in our study. Because sepsis caused by varying diseases has different characteristics, some associations have launched more specific sepsis definitions for different diseases, such as sepsis definitions for burns and surgical patients^[8,28].

In 2003, ESICM, SCCM and ISF launched the “Sepsis Rescue Campaign”, which asked doctors to increase understanding and relevant knowledge about sepsis^[29]. However, the surveys about the knowledge of doctors and nurses about sepsis guidelines indicated that doctors and nurses had poor cognition and compliance about symptoms and signs, as well as about the treatment of sepsis^[30–32]. Numerous studies confirm that early targeted therapy developed by the sepsis guidelines can significantly reduce mortality of sepsis patients and improve prognosis^[14,33,34], which is consistent with the results of our study. Therefore, in China's western region, where there is higher sepsis morbidity and mortality, we should emphasize training for medical staff regarding sepsis guidelines, increase awareness about septic patients, especially sepsis in patients after trauma, and increase compliance with the guidelines for sepsis, all to support sepsis patients.

The limitations of this study are as follows: (1) the cross-sectional study ignored the impact of seasonal factors on sepsis epidemiology, which would require prospective, randomized controlled trials for further study; and (2) we followed up only on 28-day mortality, not the ultimate mortality, and we did not analyze the specific cause of death.

Conflict of interest statement

The authors report no conflict of interest.

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